Statistical Analysis Plan Amendment 2

Study ID: 205214

Official Title of Study: A Phase 3, Open-label, Multicenter Study to Evaluate Long-term Immunogenicity and Boostability of Immune Responses in Adults who Received Different Primary Vaccination Regimens of Pre-exposure Prophylaxis with Purified Chick-Embryo Cell Rabies Vaccine Administered Concomitantly or Separately from a Japanese Encephalitis Vaccine

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STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Open-label, Multicenter Study to Evaluate Long-term Immunogenicity and Boostability of Immune Responses in Adults who Received Different Primary Vaccination Regimens of Pre-exposure Prophylaxis with Purified Chick-Embryo Cell Rabies Vaccine Administered Concomitantly or Separately from a Japanese Encephalitis Vaccine
Study Number:	RABIES-018 BST:017 (V49_23E1)
Protocol Version and Date:	Protocol Amendment 2 - 25 February 2019
Phase of Development:	Phase 3
Plan Prepared by:	PPD
Plan Amended by	PPD
Version and Date:	Amendment 2: 23 Feb 2022
Approvers:	PPD, Lead Statistician

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BMI	Body Mass Index
CI	Confidence Interval
CRDL	Clinical Research & Development Lead
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
GMC	Geometric Mean Concentration
GMR	Geometric Mean Ratio
HR	Hazard Ratio
ICH	International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IM	Intramuscular
JE	Japanese Encephalitis
KM	Kaplan Meier Curve
MCAR	Missing Completely At Random
MedDRA	Medical Dictionary for Regulatory Activities
PCEC	Purified Chick Embryo Cell-Culture
PD	Protocol Deviation
PDMP	Protocol Deviation Management Plan
PPS	Per Protocol Set

PrEP	Pre-exposure Prophylaxis
PT	Preferred Term
RVNA	Rabies Virus Neutralizing Antibody
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDD	SAS Drug Development
SDL	Study Delivery Lead
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFL	Tables, Figures and Listings
TOC	Table of Content
WHO	World Health Organization

1. BACKGROUND AND RATIONALE

Data on persistence of adequate antibody concentrations (i.e. ≥0.5 IU/mL) for up to two years after immunization with *Rabipur* (Rabies, whole virus vaccine) was found in a limited number of pre-exposure prophylaxis (PrEP) studies where the conventional (vaccine administered on days 0, 7, 21 or 28) regimen was administered. There are no data available in literature about persistence of RVNA concentrations following the new, accelerated, one-week (vaccine administered on days 0, 3, 7) PrEP regimen. According to World Health Organization (WHO), booster doses are generally required every 2-5 years and there is no evidence on the best timing for booster administration after 5 years. For this reason, the onset, extent and duration of (sero)protection and the requirement for and timing of booster vaccination following a primary series according to an accelerated or a conventional PrEP Intramuscular (IM) regimen deserves further investigation.

The aim of this study is to evaluate the long-term (up to approx.10 years) persistence and to assess the boostability of immune responses in subjects who received a primary series of accelerated or conventional rabies PrEP IM regimen in V49_23 study.

For further details please refer to section 1.0 of the protocol.

History of changes:

Date	Description	Protocol Version
25 September 2015	First version	Version 1 – 23 February 2015
11 June 2019	Second version/amendment 1: Addition of a mixed model to account for repeated measures within subjects, with inclusion of SAS code. Extension of ±14 days of the annual Scheduled Clinic Visit window for inclusion of subjects in the Per Protocol Set. Addition of details about subject disposition tables for the purpose of the Interim Analysis. Imputation method of immunogenicity data collected after the administration of a booster dose with application to the long persistence analysis. Modification of the protocol deviations and corresponding PD codes (to fit GSK codes). Details on how to deal with subjects who received a rabies booster dose after conclusion of V49_23 and beginning of V49_23E1 studies. Modification of information regarding the survival analysis: FAS-2 definition, SAS code.	Protocol Amendment 2 – 25 February 2019

Date	Description	Protocol Version
23 Feb 2022	Amendment 2: Inclusion of subjects that received a booster dose between the parent study V49_23 and the current extension study in the FAS-1 booster analysis set. Addition of booster persistence analysis	Protocol Amendment 2 – 25 February 2019

2. OBJECTIVES

Primary Objectives:

Immunogenicity Objectives:

1. To compare the long-term (up to approx.10 years) persistence of antibody responses (i.e. time until antibody concentrations drop below 0.5 IU/mL) in subjects who received a primary series of accelerated or conventional rabies PrEP IM regimen in the parent study V49_23.
2. To evaluate the antibody responses to a booster dose of Purified Chick Embryo Cell-Culture (PCEC) rabies vaccine administered to subjects with Rabies Virus Neutralizing Antibody (RVNA) concentrations < 0.5 IU/mL following a primary series of accelerated or conventional rabies PrEP IM regimen in the parent study V49_23.

Safety Objective:

To evaluate the safety of a booster dose of PCEC rabies vaccine following a primary series of accelerated or conventional rabies PrEP IM regimen in the parent study V49_23.

Secondary Objective:

Immunogenicity Objective:

To evaluate the long-term (up to approx.10 years) immunogenicity in subjects who received a primary series of accelerated or conventional rabies PrEP IM regimen in the parent study V49_23.

3. STUDY DESIGN

This is a phase 3, open-label, non-randomized multicenter, extension study in healthy adults. In the parent study (V49_23) subjects from ≥18 years to ≤65 years of age were randomized to one of four vaccination groups, three of which for rabies pre-exposure prophylaxis according to conventional (1.0 mL dose of PCEC rabies vaccine administered IM on each of days 1, 8 and 29) regimen, alone or in combination with Japanese Encephalitis (JE) vaccination according to the study group (see Table 1 below) or to a new, one-week, accelerated (1.0 mL dose of PCEC rabies vaccine administered IM on each of days 1, 4 and 8) regimen in combination with JE vaccination.

Table 1 Vaccine Groups in Studies V49_23 and V49_23E1

V49_23 study			V49_23E1 study	
Arm Code (Arm)	**Study Vaccine Group N of subjects who received full PrEP and completed the study**	**Regimen of Primary Vaccine Administration**	**Study Vaccine Group (from V49_23) Maximum N of subjects who will be invited for enrollment**	**Regimen of Booster Vaccination**
A (Conv-R/JE)	Conventional Rabies + JE vaccination N=158 subjects	**Rabies PrEP** Days 1, 8 and 29 **JE primary series** Days 1 and 29	Conv-R/JE N= up to 158 subjects	A single PCEC rabies booster dose (1.0 mL) IM for subjects with RVNA concentrations <0.5IU/mL
B (Acc-R/JE)	Accelerated Rabies + JE vaccination N=209 subjects	**Rabies PrEP** Days 1, 4 and 8 **JE primary series** Days 1 and 8	Acc-R/JE N= up to 209 subjects	A single PCEC rabies booster dose (1.0 mL) IM for subjects with RVNA concentrations <0.5IU/mL
C (Conv-R)	Conventional Rabies N=211 subjects	**Rabies PrEP** Days 1, 8 and 29	Conv-R N= up to 211 subjects	A single PCEC rabies booster dose (1.0 mL) IM for subjects with RVNA concentrations <0.5IU/mL
D (Conv-JE)	Conventional JE N=52 subjects	**JE primary series** Days 1and 29	NA	NA

Source: Table 3.1-1 of Protocol Amendment 2 (25 FEB 19)

Subjects who were randomized into one of the 3 rabies vaccination groups (arms A, B and C) of the parent study V49_23, who received the full PrEP rabies regimen and completed V49_23 study following study protocol will be invited to take part to this study.

Subjects who were randomized to the JE conventional group (arm D) in the parent study V49_23 will not be invited to take part to this extension study.

Subjects will receive their booster doses based on their individual antibody concentrations measured over time, i.e., booster will be administered only to those subjects with RVNA concentrations <0.5 IU/mL.

Blood samples will be drawn in all subjects on extension study Day 1 (i.e. approximately three years [Year 3] after completion of rabies primary series in the parent study V49_23) and then at subsequent year intervals from extension study Day 1 (Year 3) onwards (Year 4, 5, 6, 7, 8, 9 and 10 after primary series in the parent study V49_23), to investigate the kinetics of RVNA concentrations.

For further details please refer to section 3.0 of the protocol.

Table 2 Times and Events Table(s) - Scheduled Clinic Visits: For All Subjects

Visit Type		Scheduled Clinic Visit							Final Scheduled Clinic Visit
Study Period		Day 1 Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Visit Window (Days) *		n/a	-28 to +28	-28 to +28	-28 to +28	-28 to +28	-28 to +28	-28 to +28	-28 to +28
Visit Number		1	2	3	4	5	6	7	8
Study Event	**Protocol references**								
Screening and Safety									
Informed Consent [a]	Section 5.1.1	X							
Medical History	Section 5.1.2	X	X	X	X	X	X	X	X
Physical Exam[d]	Section 5.1.2	X	X	X	X	X	X	X	X
Exclusion/Inclusion Criteria	Section 4.0	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	Sections 5.1.2 and 6.5	X							
Assess SAEs and Relevant Medications [b]	Sections 7.1.4, 5.1.2 and 6.5		X	X	X	X	X	X	X
Observe for at Least 15 Minutes Post Blood Draw and Assess AEs (if any)	Section 7.1.3	X	X	X	X	X	X	X	X
Immunogenicity									
Serology Blood Draw	Section 3.5	X	X	X	X	X	X	X	X
Study Completion Procedures									
Study Termination [c]	Section 5.5								X

[a] Confirm consent form signed prior to any procedures.

[b] SAEs and the associated concomitant medications will be collected ONLY from those subjects who will receive booster vaccine during the Ad hoc Clinic Visit, starting from the time of booster administration until completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier).

[c] Subjects who terminate the study early are recommended to complete certain study-related procedures. See Section 5.5 of the Protocol Amendment 2 for further details.

[d] Physical exams have to be done by practitioners in accordance with their institutional policy. Should the physical assessment reveal any abnormal values or events, which fall under definition of SAE, these must be documented in the CRF Adverse Events Form and reported to sponsor.

*Visit 1 date to be used as reference for calculating next visit date (e.g. V1: 31 JAN 15, V2: 31 JAN 16 ± 28 days, V3: 31 JAN 17 ± 28 days). Additional 14 days will be added to the time window for the inclusion to the PPS (time window will be ± 42 days).It was deemed that additional 14 days would not impact the analysis of immunogenicity persistence.

Table 3 Times and Events Table(s) - Ad hoc and Additional Clinic Visit

Visit Type		Clinic Visit													
		Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]	Ad hoc[a]	Addi-tional[b]
Study Period		Year 3, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 1	Year 3, 7 days after Ad hoc Clinic Visit 1.1	Year 4, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 2	Year 4, 7 days after Ad hoc Clinic Visit 2.1	Year 5, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 3	Year 5, 7 days after Ad hoc Clinic Visit 3.1	Year 6, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 4	Year 6, 7 days after Ad hoc Clinic Visit 4.1	Year 7, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 5	Year 7, 7 days after Ad hoc Clinic Visit 5.1	Year 8, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 6	Year 8, 7 days after Ad hoc Clinic Visit 6.1	Year 9, ***between*** 6 ***to 9*** months after Scheduled Clinic Visit 7	Year 9, 7 days after Ad hoc Clinic Visit 7.1
Visit Window (Days)		n/a	-1 to +1	n/a	-1 to +1	n/a	-1 to +1	n/a	-1 to +1	n/a	-1 to +1	n/a	-1 to +1	n/a	-1 to +1
Visit Number		1.1	1.2	2.1	2.2	3.1	3.2	4.1	4.2	5.1	5.2	6.1	6.2	7.1	7.2
Study Event	**Protocol references**														
Medical History[c]	Section 5.1.2	X		X		X		X		X		X		X	
Physical Exam[c]	Sections 5.1.2 and 5.2	X		X		X		X		X		X		X	
Pregnancy Test[c, d]	Sections 3.5 and 5.1.2	X		X		X		X		X		X		X	
Verification of Relevant Exclusion/Inclusion Criteria[c]	Section 4.0	X		X		X		X		X		X		X	
Vaccination[e]	Section 5.2	X		X		X		X		X		X		X	
30 Minutes Post Booster Injection Assessment	Section 5.2.1	X		X		X		X		X		X		X	
Assess SAEs and Relevant Concomitant Medications[f]	Sections 7.1.4, 5.1.2 and 6.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity															
Serology Blood Draw	Section 3.5		X		X		X		X		X		X		X
Observe for at Least 15 Minutes Post Blood Draw and Assess AEs (if any)	Section 7.1.3		X		X		X		X		X		X		X

[a] Ad hoc Clinic Visit (which is planned to occur as soon as the results of the antibody assay will be available and within approximately 6 months from the blood draw taken during a previous "Scheduled Clinic Visit") is only applicable for those subjects with RVNA concentrations <0.5 IU/mL during this extension study. See sections 3.1 and 3.9 of Protocol Amendment 2 for further details.

[b] Additional Clinic Visit (within approximately 7 days from Ad hoc Clinic Visit) only applicable for subjects who will receive a booster dose of PCEC rabies vaccine during Ad hoc Clinic Visit.

[c] Procedure to be performed prior to vaccination. Physical exams have to be done by practitioners in accordance with their institutional policy. Should the physical assessment reveal any abnormal values or events, which fall under definition of SAE, these must be documented in the CRF Adverse Events Form and reported to sponsor.

[d] Only for female subject of childbearing potential who are eligible to receive the booster dose.

[e] GSK Biologicals' Randomization System on Internet (SBIR) will be used for Treatment allocation.

[f] SAEs and the associated concomitant medications will be collected starting from the booster administration and until the completion of safety follow-up period (the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier).

4. RANDOMIZATION AND BLINDING

4.1. Method of Group Assignment and Randomization

This is a non-randomized extension study. Subjects previously enrolled in V49_23 study who completed the parent study and are eligible for participation to V49_23E1 study will be identified with a unique Subject ID which is the same they were assigned to during V49_23 study.

For the purpose of the analysis, the arm's name (i.e., Vaccine group) will be the same as in parent study.

Subject will receive a booster dose depending on RVNA concentrations at Scheduled Clinic Visits 1 to 7.

For further details please refer to section 5.1.4 of the Protocol Amendment 2 (25 FEB 19).

4.2. Blinding and Unblinding

Not Applicable.

5. SAMPLE SIZE AND POWER CONSIDERATIONS

No sample size and power analysis was performed for this extension study.

Expected sample size is taken from the number of subjects enrolled in V49_23, assigned to a *Rabipur* vaccine group (i.e., Arms A, B and C), who correctly received the vaccination, completed V49_23 study according to protocol and meet all inclusion criteria and none of the exclusion criteria for this extension study.

6. DETERMINATION OF PROTOCOL DEVIATIONS

6.1. Definition of Protocol Deviations

Major Protocol Deviations (PDs) are defined in GSK WKI_9000059839 as:

- All PD leading to exclusion from analysis population.
- Any protocol deviations which are not leading to exclusion but meet the definition of Major/Critical issue (as per SOP_9000036818).

All major PDs will be evaluated before database lock and classified according to International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) into the following nine categories:

- Fraudulent data (PD code 800)

- Informed consent (PD code 900 & 910)
- Eligibility criteria not met (PD code 2010)
- Assessment or time point completion (PD code 2120 & 2090)
- Study procedures (PD code 2120)
- Excluded medication, vaccine or device (PD code 2040)
- Wrong study treatment/administration/dose (PD code 1070, 1080 & 1090)
- Failure to report safety events per protocol (PD code 2150)
- Study procedures (PD code 2100, 2120 & 2130)

Details of the PD among these categories can be found in the table in the section 7.7. Major PDs will lead to exclusion of the subject or part of the subject's data from at least one analysis set. One exception is annual visit out of window; it was decided to include in the PPS also subjects who attended the annual Scheduled Clinic Visit ± 14 days beyond the allowed time window. It was in fact deemed that additional 14 days would have no impact on the long-term immunogenicity persistence.

The number of subjects in any and by PD category will be summarized by vaccine group, center and overall. Individual subject listings will be provided in an appendix, sorted by subject and by PD category.

Prematurely terminating study participation for reasons such as withdrawal of consent or occurrence of adverse events (including death) is not considered as a PD.

6.2. Determination of Protocol Deviations

Identification of PDs will be done according to the Protocol Deviation Management Plan (PDMP, SOP_9000063106), WKI_130050 and SOP_9000059839.

Periodic Protocol Deviation review will be held as defined in the PDMP. Prior to these periodic meetings all PD trackers for manually identified protocol deviations will be merged with those identified programmatically.

After the review consolidated tracker will be uploaded to SAS Drug Development (SDD) as reference for next review meeting.

7. ANALYSIS SETS

Analysis sets are defined for each study objective and type of analysis.

7.1. All Enrolled Set

All screened subjects who provide informed consent and provide demographic and/or other baseline screening measurements.

Demography and baseline characteristics tables as well as subject listings will be produced on the All Enrolled Set.

7.2. Exposed to Booster dose

All subjects who receive at least one dose of booster during trial.

7.3. Full Analysis Set (FAS), Immunogenicity

FAS-1: Booster immunogenicity analysis

All subjects in the Enrolled Set who receive at least one booster dose during the trial (because RVNA value below 0.5 IU/mL at scheduled visit) or before entering the trial (e.g. travellers to endemic areas or veterinarians who got the booster regardless of the RVNA value) and provide immunogenicity data.

FAS-2: Long term immunogenicity analysis

All subjects in the Enrolled Set who provide immunogenicity data.

Note: In the long-term immunogenicity analysis, when a subject receives a rabies vaccine booster dose (before or during the study) because RVNA value is below 0.5 IU/mL, subsequent RVNA values after the booster dose will be set to half of the detection level (i.e. 0.1 IU/mL) until study end even if the subject withdraws earlier than last study visit (see last part of section 8.2 for a detailed explanation).

In case a subject receives a booster dose before or after entering the study (e.g. travellers to endemic areas, veterinarians) but the last known RVNA value was above 0.5 IU/mL, then he/she will be excluded from the long term immunogenicity analysis set (i.e. FAS-2 and PPS). This is justified by the fact that including actual values as recorded after the booster dose would inflate the immunogenicity persistence; on the other hand, it would be inappropriate to apply the same rule used for subjects receiving a booster dose when RVNA value is less than 0.5 IU/mL as this is not the case.

7.4. Per Protocol Set (PPS), Immunogenicity Set

PPS-1: Booster immunogenicity analysis:

All subjects in the FAS-1 Immunogenicity who:

- Have no major PD leading to exclusion (see section 6.2)
- Are not excluded due to other reasons such as withdrawal of consent (see section 6.2)

PPS-2: Long term immunogenicity analysis:

All subjects in the FAS-2 Immunogenicity who:

- Have no major PD leading to exclusion (see section 6.2)

- Are not excluded due to other reasons such as withdrawal of consent (see section 6.2)

Immunogenicity analyses will be repeated on PPS if it differs from FAS for more than 10% (by objective).

7.5. Safety Set

Safety Set

All subjects who are exposed to booster dose and report safety data.

7.5.1. Restricted Safety Set

Not applicable

7.6. Other Analysis Set

None

7.7. Overview of Analysis Sets by PD Code

Table 4 Safety Sets: applicable to Exposed to Booster dose subjects only

PD code	PD Description and Exclusion Reasons	Study Objective/ Period	*Exposed Set*	*Safety Set*
	Exclusion code		***EXPFL***	***SAFFL***
1070	**incomplete treatment course. Booster was not administered although subject had RVNA concentration of <0.5 IU/mL**	***All Study***	*EXC*	*EXC*
2150	**Subject did not provide any post-booster safety data**	***Approx. 6 months after booster exposure****		*EXC*

* For further details refer to study protocol
EXC = excluded from this analysis set.

Table 5 Immunogenicity Sets

PD code	PD Description and Exclusion Reasons	*All ENROLLED*	*FAS 1*	*FAS 2*	*PPS 1*	*PPS 2*
	Exclusion code	***ENRFL***	***FAS10FL***	***FAS20FL***	***PPS10FL***	***PPS20FL***
800	**Fraudulent data**	EXC	EXC	EXC	EXC	EXC
900	**Signed informed consent not available on site**				EXC	EXC
900	**Wrong informed consent version signed**				EXC	EXC
900	**Informed consent not signed and/or dated by subject**				EXC	EXC
900	**Informed consent not signed and/or dated by appropriate site staff.**				EXC	EXC
900	**Informed consent not signed prior to any study procedure (examples: a, b, c)**				EXC	EXC
900	**Other informed consent deviations**				EXC	EXC
910	**Partially or inappropriately signed ICF**				EXC	EXC
1070	**Booster was administered although subject had RVNA concentration ≥0.5 IU/mL**			EXC	EXC	EXC
1070	**Route of administration is wrong or unknown**				EXC	
1070	**Administration of booster vaccine at wrong visit**				EXC	
1070	**Commercial vaccine used in place of study vaccine (but same vaccine)**				EXC	
1070	**Study treatment administered while contraindication**				EXC	
1070	**Study treatment not prepared as per protocol (e.g. reconstitution)**				EXC	
1070	**Incorrect Volume was given**				EXC	
1080	**Use of study treatment impacted by a temperature excursion which was not reported or approved, or which was disapproved for further use.**				EXC	
1090	**Expired study treatment administered**				EXC	
2010	**Eligibility Criteria Not Met**				EXC	EXC
2040	**Prohibited concomitant medication (interval + type)**				EXC	EXC
2040	**Prohibited concomitant vaccination (interval + type)**				EXC	EXC

PD code	PD Description and Exclusion Reasons	*All ENROLLED*	*FAS 1*	*FAS 2*	*PPS 1*	*PPS 2*
	Exclusion code	***ENRFL***	***FAS10FL***	***FAS20FL***	***PPS10FL***	***PPS20FL***
2040	**Other excluded medication, vaccine or device deviation**				EXC	EXC
2090	**Blood draw after booster dose outside 7 (+/- 1 day) day interval**				EXC	EXC
2090	**Did not comply with blood draw schedule (for annual Scheduled Clinic Visits): yearly blood draw outside +/- 42 days interval**				EXC	EXC
2100	**PII recorded in label of sample**		EXC	EXC	EXC	EXC
2100	**Low volume (not sufficient to perform testing**		EXC	EXC	EXC	EXC
2100	**No samples collected for subject (and should have been collected)**		EXC	EXC	EXC	EXC
2100	**Mislabelling (sample not tested)**		EXC	EXC	EXC	EXC
2100	**Serological results not available**		EXC	EXC	EXC	EXC
2120	**Assessment not properly performed**				EXC	EXC
2120	**Temperature deviation from range defined in protocol and/or SPM/lab manual - --18 to -12C Freezer**				EXC	EXC
2120	**Incorrect spinning/processing of sample**				EXC	EXC
2120	**Central/internal/external lab deviations**				EXC	EXC
2120	**Mislabelling (sample tested)**				EXC	EXC
2130	**Testing performed on samples not aligned with ICF**				EXC	EXC

FAS = Full Analysis Set; PPS=Per Protocol Set; EXC = excluded from this analysis set.

8. GENERAL ISSUES FOR STATISTICAL ANALYSES

8.1. Adjustment for Covariates

Cox proportional hazards regression model – Time to first RVNA <0.5IU/mL

The hazard ratio (HR) from the Cox (Andersen, 1982) proportional hazards regression model will be used as a treatment effect measure for time to event endpoints.

Group comparisons for first occurrences of a booster (i.e., RVNA concentration <0.5 IU/mL) will be performed using an adjusted Cox proportional hazard regression model with effect for treatment and center. Ties will be handled with the exact method as it assumes that there is a true but unknown ordering for the tied event times.

Analysis of Variance (ANOVA) – Analysis of boostability.

For subjects who will receive rabies vaccine booster the log-transformed antibody concentration at day 7 will be analyzed using an Analysis of Variance (ANOVA) which includes treatment (vaccine received at time of parent study V49_23) and center. Summary tables will show adjusted GMCs and GMR for each treatment and adjusted ratios of GMCs between vaccine groups.

Mixed model for repeated measures – Analysis of persistence

Log-transformed antibody titers as collected at annual Scheduled Visits (from Visit 1 to Visit 7) will be analyzed using a mixed model for repeated measures within subject, including time and treatment as independent variables, their interaction and a random intercept with an unstructured covariance matrix.

8.2. Handling of Dropouts, Missing Data

Time to event analysis:

The Cox proportional hazards regression model analysis will be based on methods for right-censored data (Lindsey, 1998).

In this setting, the event/failure will be represented by having a RVNA concentration <0.5 IU/mL (see section 8.8). Subjects without event (with missing blood draw, or lost to follow up or early terminated) will be regarded as right-censored data.

GMC and percentage analysis - boostability:

To evaluate the booster response in terms of Geometric Mean Concentration (GMC), Geometric Mean Ratio (GMR) and percentage of subjects with RVNA concentration ≥0.5 IU/mL; missing data will be not included in the analysis.

GMC and percentages of subjects with RVNA concentrations ≥ 0.5 IU/mL

To evaluate the long-term (up to approx.10 years) immunogenicity in subjects who received a primary series of accelerated or conventional rabies PrEP n the parent study (V49_23) in terms of GMC and percentage of subjects with RVNA concentration ≥0.5 IU/mL; missing data as such will be not included in the analysis. If a subject receives a rabies vaccine booster dose, the RVNA value after booster will be set to half of quantification level from that moment onward. This because the exposure to a booster dose during the trial introduces a bias, as the RVNA concentrations will reflect the booster response and not the long-term persistence after the primary series (i.e., vaccination received at time of parent study).

8.2.1. Safety Data

Safety data (i.e., unsolicited serious adverse events) will be collected and analyzed only for subjects who will receive at least one booster dose during the trial.

No imputation methods will be used to address missing values.

8.2.2. Immunogenicity Data

Immune response in subjects with or without booster will exclude missing values, assuming missing immunogenicity values as Missing Completely At Random (MCAR) and therefore will not contain information that impact the result of the analysis (i.e., not informative).

Imputation methods will be used for those subjects who will receive a booster dose during the trial i.e., once the RVNA concentration fall below the predefine cut-off of 0.5 IU/mL, that value will be set up to half of quantification level from that moment onward.

8.3. Multicenter Studies

Long-term persistence of antibody responses after primary series

Both time-to-event and persistence analyses will include term for center.

Boostability analysis

Geometric mean concentration analysis will be estimated using a two-way ANOVA including treatment and center.

If the statistical model does not converge due to the factor “center”, a model without center effect will be fitted instead.

8.4. Multiple Comparisons and Multiplicity

No adjustment was made due to multiplicity.

8.5. Immunogenicity Subsets

Descriptive statistics of RVNA persistence following a booster dose administration will be carried out at the end of the study. This will include subjects in the FAS-1 aggregated by year of booster receipt: i.e. subset FAS-1 year 3, FAS-1 year 4 and so forth.

8.6. Subgroups

Not Applicable.

No subgroup analysis will be performed but a contingency table analysis will be created counting the frequency of subjects who receive 0 booster dose, 1, 2, 3 or more booster doses.

8.7. Data Transformation

Distributions of antibodies are generally skewed to the right (Nauta, 2010). Therefore, antibody concentrations will be log10-transformed. GMCs and their 95% Confidence Intervals (CIs) are computed by exponentiating (base 10) the least squares means and 95% CIs of the log10 concentrations.

8.8. Derived and Computed Variables

Data from parent study (V49_23)

Time to event analysis

For time to event analysis (i.e., Kaplan-Meier (KM) and Cox proportional hazard regression model), immunogenicity data from parent study, from day 57 up to one year, as well as data related to time between the end of parent study and start of this study (i.e., if subject receives a booster between the two studies) will be considered, as estimation of time to RVNA concentration drop below 0.5IU/mL.

Long term immunogenicity analysis

Demographics

Race and Age at time of V49_23 enrolment will be derived from demography of the parent study.

Body Mass Index (kg/m^2) (BMI) will be calculated using the following formula: Weight (kg) / Height^2 (m^2)

Time to Event

Survtime represents time to event/censoring in years:

Survtime variable will be derived using the planned visit day at which the event occurred or the subject is censored as time point.

The following SAS code describes how to derive **Survtime** from V49_23 study and from the current study (V49_23E1).

```
DATA <dbname>;
  SET <dbname>;
IF LBORRES IN ('<0.1', '0.1', '0.2', '0.3', '0.4')
THEN DROP ='Y';
ELSE DROP ='N';
format LABEL $12.;
IF STUDYID = 'V49_23' THEN DO;
    IF VISITNUM = 9  THEN do;POINT =1; YEAR =57; LABEL = 'Day 57'; end;
    IF VISITNUM = 10 THEN do;POINT =2; YEAR =91; LABEL = 'Day 91'; end;
    IF VISITNUM = 11 THEN do;POINT =3; YEAR =181; LABEL = 'Day
181';end;
    IF VISITNUM = 12 THEN do;POINT =4; YEAR =365;LABEL = 'Day 366';end;
  END;
END;
IF STUDYID = 'V49_23E1' THEN DO;
    IF VISITNUM = 1 THEN do; YEAR = 3*365;  LABEL = 'Year 3'; end;
    IF VISITNUM = 2 THEN do; YEAR = 4*365;  LABEL = 'Year 4'; end;
    IF VISITNUM = 3 THEN do; YEAR = 5*365;  LABEL = 'Year 5'; end;
    IF VISITNUM = 4 THEN do; YEAR = 6*365;  LABEL = 'Year 6'; end;
    IF VISITNUM = 5 THEN do; YEAR = 7*365;  LABEL = 'Year 7'; end;
    IF VISITNUM = 6 THEN do; YEAR = 8*365;  LABEL = 'Year 8'; end;
    IF VISITNUM = 7 THEN do; YEAR = 9*365;  LABEL = 'Year 9'; end;
    IF VISITNUM = 8 THEN do; YEAR = 10*365; LABEL = 'Year 10';end;
END;
Survtime= YEAR;

IF DROP ='Y' THEN CENSOR=1; ELSE CENSOR = 0;

RUN;
```

Censor: represents censoring indicator variable: 0=censored, 1=event of interest;

Event of interest: RVNA concentration < 0.5 (censor=1)

If one of the followings occur, subject will be censored (censor=0) and time to the last data available strictly before the event will be included in the survival analysis:

- Subject is lost to follow up
- Subject withdraws consent
- RVNA concentration not available for last visit (last visit could differ from the final visit)
- Subject receives booster (study vaccine or another rabies vaccine) but RVNA concentration ≥ 0.5 or unknow
- Subject performs final visit (i.e., study termination visit) and RVNA concentration is ≥ 0.5IU/mL (for the purpose of the IA, if visit 4 is completed by the subject he will be considered as a censored value at the time of visit 4)

The subjects will be considered as censored if any of the following event occurs before the subject's antibody titer level goes beyond the level of 0.5IU/mL:

- All further blood draw results are missing

Censor variable will be set to 0 if any of the case above occurs. If the subject's antibody level titer goes beyond 0.5 IU/mL censoring values will be set to 0 at the time of the 1st antibody titer level below 0.5 IU/mL.

Point Variable describes the order of RVNA concentration observed. It will be POINT= 5 if a subject receives booster between V49_23 END (last visit date) and V49_23E1 START (first visit date).

Immunogenicity

Values below the limit of quantification (recorded as "< LQ") will be set to half that limit (i.e., LQ/2]).

Geometric Mean Concentration

The GMC will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers/concentrations.

Geometric Mean Ratio

Geometric mean ratios (GMRs) measure the changes in immunogenicity concentrations *within* subjects.

The GMR will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}\left(v_{ij}/v_{ik}\right)}{n}\right\}} = 10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(v_{ij})-\log_{10}(v_{ik})}{n}\right\}}$$

where, for n subjects, v_{ij} and v_{ik} are observed immunogenicity titers/concentrations for subject i at time-points j and k, $j \neq k$.

Imputation of RVNA concentration in subjects receiving a booster

Once a subject receives a rabies vaccine booster dose (i.e. RVNA<0.5) he/she will be treated as follows:

Time to event analysis:

Censor=1 for the time-point in which RVNA is observed being below 0.5 IU/mL

All further subject immunogenicity data will not be used for Time to event analysis.

GMC and percentage analysis - boostability:

Subject is included in the Exposed to Booster Set and independently on time or visit in which booster is administered the time-points will be as following:

- Pre-booster
- 7 days after booster
- 6 to 9 months after booster

Long-term persistence of antibody responses after primary series

All immunogenicity data until booster will be part of analysis as they are reported.

For subjects receiving a booster dose, the following method of imputation will be used for antibody values:

- Values, missing or not, will be replaced with half of the quantification level (0.1 IU/mL) from that moment onward.

Subjects receiving a booster dose outside of the study and for which RVNA value at the time of booster vaccination is not available will be excluded from FAS-2 and PPS-2 (see section 7.3 for details)

Duration in the Study

Duration in the study is defined in days as:

Last visit date (visit x)[a] – Enrollment date (visit 1) + 1

[a] or premature discontinuation date (in case of withdrawal from the study)

The duration is missing if one of the dates is missing or incomplete.

Unsolicited Serious Adverse Events

All serious adverse events (AEs) following *Rabipur* booster dose within the study will be characterized according to the date of occurrence related to the vaccination phase as follows:

- **Emergence before vaccination phase**: start date before the first date of injection of study vaccine.
- **Emergence during vaccination phase**: start date on or after the first date of injection of study vaccine or, adverse event increase in severity including to "serious" AE.

If start date is equal to the first date of injection then "timing" variable ("On injection day, before injection"/"On injection day, after injection") will be used to define whether the adverse event occur before or after the injection.

If an AE start date is missing or unknown, the AE will be considered as emergent.

When start and/or end dates of an AE are only partially known, AEs will be categorized as emergent before, during, or after vaccination phase using the following rules:

- If the partial end date is before (<) the first study vaccination (i.e., year or year & month is/are before the first study vaccination year or year & month) then the AE is emergent before vaccination phase.
- If the partial start date is equal or after (≥) the first study vaccination (i.e., year or year & month is/are after or the same as the first study injection year or year & month) then the AE is emergent during vaccination phase.

The **maximum event severity** is the greatest severity associated with a preferred term (PT) for a reported AE according to the following order: Mild < Moderate < Severe. Unknown/ Missing severity is considered as severe (except for the definition of emergence).

Multiple AEs with the same PT for the same subject are counted only once.

Vaccination-related AEs are those for which the cause has been evaluated by the investigator, and recorded either as possibly related, probably related or unknown/ missing.

Pre-study, Concomitant and Post-Vaccination Medications

A **prior medication** is a medication received by the subject prior to the start of V49_23E1 (i.e. Termination visit date for V49_23 ≤ medication start date < start of this extension study V49_23E1).

A **concomitant medication** will include drugs (antipyretics and/or analgesic medications within 24 hours prior to vaccination) and all medications (including vaccines) from the time of the boost per administration until the day of next Scheduled Clinic Visit. (i.e. medication start date ≥ booster administration date).

Concomitant medications, as defined in study protocol, include all medications (including vaccines) taken by/administered to subjects who experienced Serious Adverse Events (SAEs) during the safety follow up period (which is, the day of the next Scheduled Clinic Visit after booster vaccination or the date of Early Termination Visit, whichever is earlier) after administration of the rabies vaccine booster dose. In case of start date of a medication intake is missing, the medication is considered as concomitant.

8.9. Analysis Software

All analyses will be performed using SAS Software version 9.2 or higher.

9. STUDY SUBJECTS

9.1. Disposition of Subjects and Withdrawals

All subjects who successfully completed rabies PrEP regimens in V49_23 and did not have protocol deviations which can impact the immunogenicity response (e.g., wrong vaccination), and who provide informed consent will be accounted for in this study. The frequencies and percentages of subjects in each analysis set, study withdrawals, and protocol deviations will also be presented.

For the purpose of the IA subject disposition will be summarized for the three following analysis sets: from All enrolled set to FAS-2 set, from FAS-2 set to PPS-2 set and eligible for booster dose to exposed to booster dose set.

The time the subjects are under observation will be summarized by vaccine group and overall using summary statistics (mean, SD, minimum, median, maximum)

10. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

In general, all tables presented in CSR section 14.1 should show a Total column across vaccine groups.

10.1. Demographics

As demographic characteristics the following variables will be summarized by reporting the mean, standard deviation, median and range, and will be calculated by vaccine group and overall:

- Age at time of first exposure (i.e., enrolment in study V49_23).
- Height, weight, and BMI at time of extension study enrolment (i.e., enrolment in V49_23E1)

The frequencies and percentages of subjects by sex, country, age categories (for posting), race, entry criteria fulfilled and booster received before entering in to the study V49_23E1 will be presented by vaccine group and overall.

Demographic data will be tabulated for the All Enrolled subjects, for Exposed to Booster dose set and for FAS-2.

10.2. Medical History

The frequencies and percentages of subjects with medical history will be presented by MedDRA system organ class and PT, and by vaccine group and overall. Medical history data will be tabulated for the All Enrolled Set.

11. IMMUNOGENICITY ANALYSIS

11.1. Blood Samples

The frequencies and percentages of subjects with blood draws will be summarized overall and by vaccine group. Data will be tabulated for the All Enrolled set.

11.2. Primary Objectives Analysis

Primary Immunogenicity Objectives:

1. To compare the long-term (up to approx.10 years) persistence of antibody responses (i.e. time until antibody concentrations drop below 0.5 IU/mL) in subjects who received a primary series of accelerated or conventional rabies PrEP intramuscular (IM) regimen in the parent study V49_23.
2. To evaluate the antibody responses to a booster dose of Purified Chick Embryo Cell-Culture (PCEC) rabies vaccine administered to subjects with Rabies Virus Neutralizing Antibody (RVNA) concentrations < 0.5 IU/mL following a primary series of accelerated or conventional rabies PrEP IM regimen in the parent study V49_23.

Primary hypotheses:

There is no null hypothesis associated to primary objectives.

Time to first RVNA concentrations < 0.5 IU/mL

Cox proportional hazards regression model

Since, already at the end of the parent study (Day 366, study V49_23) it was observed a difference in the persistence of adequate RVNA concentrations between subjects who have received the accelerated PrEP schedule and those who received the conventional rabies vaccines schedule, the HR from the Cox proportional hazards regression model will be used as a treatment effect measure for time to event endpoints.

Statistical model:

An adjusted proportional hazards regression Cox model will be used:

$$h(t) = h_0(t) \cdot \exp(\beta_1 x_1 + \beta_2 x_2)$$

where:
t represents the survival time
h(t) is the hazard function as determined by the covariates treatment and center
$h_0(t)$ is the baseline hazard function at time *t*
X_1 represents treatment
X_2 represents center
β_1 and β_2 are the unknown parameters for treatment and center, to be estimated.
The HR is a multiplicative constant $\exp(\beta_1)$ comparing the hazard function in the accelerated schedule group relative to the hazard function in the conventional schedule group.

The HR will be derived from the Cox proportional hazards model using SAS PROC PHREG (with TIES=EXACT).

HR point estimate(s) will be based on partial maximum likelihood function, and Wald-test based two-sided 95% confidence intervals will be requested by the RISKLIMITS option.

The following SAS code will be applied:

```
PROC PHREG data=<dataset>;
class arm center;
MODEL survtime*status(0)=ARM center/ TIES=EXACT RISKLIMITS;
RUN;
```

survtime represents variable containing event/censoring times.

status represents censoring variable (0=censored, 1=event).

Estimation of survival functions

The term "survival function" S(t) is used here in its general meaning as probability of experiencing a specific event at time t or later. The event of interest is the time when ***RVNA concentrations < 0.5 IU/mL.***

A graphical estimate of the survival function separately for each vaccine schedule group will be obtained by the KM product - limit method as implemented in SAS PROC LIFETEST.

Together with the KM curve, the 95% CIs, will be estimated and displayed per each vaccination regimen. Standard errors of the KM estimates will be based on the Greenwood's method; 25th and 75th percentile and median survival will be provided if estimable.

Data will include observations at 7 days after primary vaccine schedule and at 3, 5 and 12 months from the parent study (V49_23) and the year observations from this study.

```
PROC LIFETEST data=<dataset> plots=(survival(atrisk) logsurv);
TIME survtime*Status(0);
STRATA arm;
RUN;
```

Immune response to booster dose

Geometric Mean Concentration and Geometric Mean Ratios (GMR)

For subjects receiving a booster dose, analysis of boostability will be conducted 7 days and 6 months after administration of the booster dose by providing GMRs and associated 95% CIs, considering the antibody value before the booster visit (i.e., 6 months before following the blood drawn during previous Scheduled Clinic Visit) as baseline (denominator) and the antibody concentration at 7 days and at 6 months after booster as the numerator.

Independently of the time (i.e., visit) a subject receives a booster dose of PCEC vaccine, RVNA concentration as detected from the blood drawn during previous scheduled clinic visit (approximately six months before the booster administration) will be consider baseline value and summarized by the mean of GMC, with associated 95% CIs, median, minimal and maximal values for each vaccine schedule group. In the same table the 7 days and 6 months post booster dose response and geometric mean ratio will be described.***Percentage of subjects with RVNA concentrations ≥ 0.5 IU/mL***

No inferential model is defined for the binomial variable (i.e., subject with RVNA concentrations ≥ 0.5 IU/mL). Percentages of subjects at 7 days and at 6 months (i.e., at subsequent Scheduled Clinical Visit) after the booster dose will be presented together with 95% CIs (Clopper, 1934) by primary vaccine schedule (arm).

11.3. Secondary Objectives Analysis

Secondary Immunogenicity Objective:

To evaluate the long-term (up to approx.10 years) immunogenicity in subjects who received a primary series of accelerated or conventional rabies PrEP intramuscular (IM) regimen in the parent study V49_23.

Yearly Geometric Mean Concentrations up to Year 10

All subjects enrolled in this extension study, independently from booster administration, are planned to be followed until year 10 from the primary vaccination.

Log-transformed antibody titers as collected at annual Scheduled Clinic Visits (from Visit 1 to Visit 7) will be analyzed using a mixed model for repeated measures within subject, including time, center and treatment as independent variables, interaction for time and treatment, a random intercept with an unstructured covariance matrix.

SAS code will look like the following:

```
PROC MIXED DATA = model;
   class subject time treatment center;
   model log_Ab = time treatment time*treatment center/ CL s ;
   lsmeans time treatment time*treatment;
   random intercept / subject = usubjid type = UN;
RUN;
```

Reverse Cumulative Distribution Figure (RCDF) up to Year 10

The percentages of subjects with concentration greater than or equal to defined RVNA values (on log10 scale) will be presented as reverse cumulative distribution curve, having the individual RVNA concentration on the X-axis and the percentage of subject with equal to or greater than the value on the Y-axis by each study visit (i.e., Year)

Note: If subject receives a booster during the study, for the purpose of the secondary objective analysis on long-term persistence of immune responses the RVNA concentration after the booster will not be 'entered' as such, but half of quantification level from that moment will be used for all consecutive visits.

11.4. Other Analysis

Analysis on subjects who received more than one booster dose

A contingency table by vaccine groups (from parent trial) will be presented, counting the frequency and the percentage of subjects receiving no booster, one booster dose, two booster doses and three or more booster doses during the extension trial.

Immunogenicity values after the second booster dose will not be used for any analyses. Subjects are kept in the study to monitor whether there is need for additional doses of vaccine in case RVNA concentrations go below 0.5IU/mL.

Analysis of booster persistence

Analogously to the long-term immunogenicity analysis, an evaluation of booster persistence will be performed using annual visit values after booster doses.

12. EFFICACY ANALYSIS

12.1. Primary Objectives Analysis

Not Applicable.

12.2. Secondary Objectives Analysis

Not Applicable.

12.3. Other Objectives Analysis

Not Applicable.

13. SAFETY ANALYSIS

The analysis of safety assessments in this study will include summaries of the following categories of safety data collected for subjects who will receive a rabies vaccine booster dose:

- Booster exposure.
- Unsolicited serious adverse events.

13.1. Analysis of Extent of Exposure

In this study only SAEs and the associated concomitant medications will be collected and only for those subjects who will be exposed to a rabies vaccine booster dose.

The period of observation for SAEs extends from the time the subject receives the booster dose until he or she completes the specified safety follow-up period (i.e the day of the next Scheduled Clinic Visit after booster vaccination or on the date of Early Termination Visit, whichever is earlier).

13.1.1. Safety Completeness Analysis

Not Applicable

13.2. Solicited Local and Systemic Adverse Events

Not Applicable

13.3. Unsolicited Adverse Events

This analysis applies only to SAEs occurring during the study and from the time of booster injection till the next Scheduled Clinic Visit (approximately 6 months after booster administration), judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in AE electronic Case Report Form (eCRF), with a start date on or after the date of booster dose. SAE starting prior to booster dose will not be recorded in the eCRFs.

The original verbatim terms used by investigators to identify SAEs in the CRFs will be mapped to PTs using the MedDRA dictionary. The SAEs will then be grouped by MedDRA PTs into frequency tables according to system organ class. SAEs judged by the investigator as at least possibly related to study vaccine will be summarized by vaccine group, according to system organ class and PT within system organ class. When an unsolicited SAE occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- Serious adverse events.
- Serious adverse events that are possibly or probably related to booster vaccination.
- Serious adverse event leading to withdrawal.
- Deaths

Data listings of all SAEs will be provided by subject. In addition, SAEs in the categories above will be provided as listed data. Only vaccine-emergent SAEs (see section 8.8 for definition) will be analyzed, i.e., excluding those eventually occurring after a subject has given informed consent but before booster vaccination.

13.4. Combined Solicited and Unsolicited Adverse Events

Not Applicable

13.5. Clinical Safety Laboratory Investigations

Not Applicable

13.6. Concomitant Medication

The frequencies and percentages of subjects reporting concomitant medications associated to treatment-emergent SAEs will be tabulated overall and by vaccine group. Medications (generic drug name) will be coded using the WHODRUG dictionary (see section 8.7 for definition).

14. INTERIM ANALYSIS

14.1. Interim Analysis

Half Way Interim Analysis

At Year 6 (i.e., visit 4, 3 years after start of this extension study) a formal interim analysis will be carried out and results will be presented in an interim Clinical Study Report (CSR).

This analysis will include both immunogenicity and safety results until visit 4.

The interim CSR might be submitted to the Health Authority in case results support indication for the booster dose at a given time after the primary regimen.

14.1.1. Futility Analysis

Not Applicable.

15. DATA MONITORING COMMITTEES

Interim analyses will be evaluated internally from the study team. No data monitoring committee (DMC) is foreseen for this extension study

16. PEER REVIEW

Not applicable

17. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

For the complete list of tables, listings and figures please refer to the Table of Contents (TOC) stored in the eTMF.

18. LAYOUT SPECIFICATIONS FOR TABLES, LISTINGS AND FIGURES

For the mock-up catalogue to be used during programming, please refer to the document stored in within the SDD server.

Since all TFLs will be produced using SAS®, the output actually generated may slightly differ from the mock-ups presented in the study specific Mock-up catalogue.

19. REFERENCES

Andersen P.K. and Gill R.D. Cox's Regression Model for Counting Processes: A Large Sample Study. The Annals of Statistics 1982; 10; 1100-1120.

Clopper CJ, Pearson ES. The use of Confidential or Fiducial Limits Illustrated in the Case of the Bbinomial. Biometrika 1934; 26:404-413.

Lindsey JC, Ryan LM (1998). Tutorial in Biostatistics: Methods for Interval-Censored Data. Statistics in Medicine 17: 219-238.

Nauta J. Statistics in Clinical Vaccine Trials. 2010. Heidelberg: Springer.